TMA DoD Pharmacoeconomic Center
Fort Sam Houston, TX

MTF Quarterly Webcast
March 8, 2011

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Director, DoD Pharmacoeconomic Center

Introduction

- Greetings from the PEC
- Purpose of the Quarterly MTF Webcast
- DCO Ground Rules
  - Type questions into the DCO system
  - Put on mute, not on hold
  - Contingency plan if DCO system quits working

Topic Outline

- Introduction from Director, PEC (LTC Spridgen)
- MTF "best practices" — Hydrocodone/APAP Substitution Program (LTC Dupuis)

- Review of November 2010 P&T Meeting (Dr Meade)
- Overview of February 2011 P&T Meeting (Dr Meade)
- Closing the Loop on Formulary Decisions (Dr Trice)
- Update on Lexicomp & Epocrates (Dr Beck)

- Procedures for Drug Recall (Dr Hellwig)

- Update on the Drug Seeking Beneficiary (DSB) Edit (Dr Hearin)

MTF “Best Practices"

Hydrocodone/APAP Substitution
Bayne-Jones Army Hospital
Fort Polk, Louisiana

LTC Joe Dupuis
Chief, Department of Pharmacy

Motivation for Substitution

- **FDA to Manufacturers:**
  - Limit APAP in prescription drugs to 325mg/tab
  - *New Boxed Warning*: Potential for severe liver injury for APAP-containing prescription products
  - Mostly APAP+ opioid combination products
  - **www.fda.gov/Drugs/DrugSafety/ucm239821.htm**
- **Reducing Hassle**
  - (Too) Many hydrocodone/APAP products on market
  - Only 3 hydrocodone doses (5mg, 7.5mg, 10mg) represented in most combination products
  - Pre-approved substitution — eliminates hassle for patient, pharmacy, and prescriber

Substitution Chart

Prescribed Product	Pharmacy Substitution
Hydrocod 5mg + APAP 300mg **(Xodol-5)**	**Hydrocodone/APAP 5/325mg**
Hydrocod 5mg + APAP 325mg **(Norco-5)**	
Hydrocod 5mg + APAP 400mg **(Zydone-5)**	
Hydrocod 5mg + APAP 500mg **(Vicodin/Lortab-5)**	
Hydrocod 7.5mg + APAP 300mg **(Xodol-7.5)**	**Hydrocodone/APAP 7.5/325mg**
Hydrocod 7.5mg + APAP 325mg **(Norco-7.5)**	
Hydrocod 7.5mg + APAP 400mg **(Zydone-7.5)**	
Hydrocod 7.5mg + APAP 500mg **(Lortab-7.5)**	
Hydrocod 7.5mg + APAP 650mg (**Lorcet Plus)**	
Hydrocod 7.5mg + APAP 750mg (**Vicodin ES)**	
Hydrocod 10mg + APAP 300mg **(Xodol-10)**	**Hydrocodone/APAP 10/325mg**
Hydrocod 10mg + APAP 325mg **(Norco-10)**	
Hydrocod 10mg + APAP 400mg **(Zydone-10)**	
Hydrocod 10mg + APAP 500mg **(Lortab-10)**	
Hydrocod 10mg + APAP 650mg **(Lorcet-10)**	
Hydrocod 10mg + APAP 660mg (**Vicodin HP)**	
Hydrocod 10mg + APAP 750mg (**Maxidone)**	

Substitution Process

- **Hydrocodone-Equivalent Substitution**
  - Example Rx:
    - Vicodin-HP #16 tabs
    - Sig: take 1 tab p.o. q6h prn pain
  - Substitution Rx:
    - Hydrocodone/APAP 10/325 #16 tabs
    - Sig: take 1 tab p.o. q6h prn pain
- **Documentation and Counseling**
  - RPh writes subst. product description (Hydrocod/APAP 10/325) next to the prescribed drug name (Vicodin-HP) and initials Rx
  - Rx Qty, Sig, and Refills are NOT altered
  - No routine patient counseling regarding the substitution
  - Avoid any suggestion that patients take supplemental APAP to “make-up the difference”
  - Chronic pain patients MUST BE counseled regarding the substitution and their pain prescriber’s approval of substitution

Substitution Pre-Approval

- **Automatic for BJACH / DENTAC Prescribers**
  - P&T Committee-approved substitution
  - 3 hydrocodone/APAP options in CHCS/AHLTA
  - Synonyms (Norco, Vicodin, Lortab, & Lorcet) linked to each hydrocodone/APAP option
- **Off-Post Prescribers**
  - Letter & substitution chart mailed to prescribers
  - Prescribers must agree to substitution
  - Sign and return authorization to pharmacy
  - JAG-approved letter and process
- **Pharmacy Maintains Pre-Approval File**

Substitution Pre-Approval

- Instructions in pre-approval request

If you would like the BJACH pharmacy to automatically substitute to the 325mg acetaminophen-dosed medication as described in the BJACH Pharmacy Automatic Substitution table, please sign, date, and return this memo in the enclosed envelope.

Attached is the BJACH Pharmacy Hydrocodone/Acetaminophen Automatic Substitution table. Please keep for your information when returning the substitution approval memo.

I authorize BJACH PHARMACY to AUTOMATICALLY CHANGE a hydrocodone/acetaminophen prescription to a HYDROCODONE EQUIVALENT, hydrocodone/acetaminophen 325mg product, as described in the BJACH Pharmacy Automatic Substitution table, below with my signature.

Provider's Signature and Date:_____

Provider's Printed Name:_____
Address:_____
Phone Number:_____

Implementation

- **Challenges**
  - Maintaining prescriber pre-approval file
  - Product similarity and mix-up potential

    Tablet imprints (Mallinckrodt generics)

5/325	M365, oblong, white tablet
7.5/325	M366, oblong, white tablet
10/325	M367, oblong, white tablet

- **Adjustments**
  - Faxing substitution approval letters on-the-spot
  - Alternate generic sources: bar-code verified product selection

Contact Information

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Review of November 2010 P&T Activities

Dave Meade, PharmD, BCPS
Clinical Pharmacist

November 2010
DoD P&T Committee Meeting

- **Uniform Formulary Class Reviews**
  - Non-Insulin Diabetes Drug Class
    - Alpha-glucosidase inhibitors (AGIs)
    - Amylin agonist
    - Biguanides
    - Dipeptidyl-peptidase 4 (DPP-4) inhibitors
    - Glucagon-like peptide-1 receptor agonists (GLP1RAs)
    - Meglitinides
    - Sulfonylureas
    - Thiazolidinediones (TZDs)

November 2010
DoD P&T Committee Meeting

- **New Drugs in Previously Reviewed Classes**
  - Doxepin tablets (Silenor)
  - Estradiol valerate/dienogest (Natazia)
  - Fenofibric acid tablets (Fibricor)
  - Hydromorphone Hydrochloride (HCl) Extended Release tablets (Exalgo)
  - Mometasone/formoterol oral inhaler (Dulera)
  - Pitavastatin tablets (Livalo)

November 2010
DoD P&T Committee Meeting

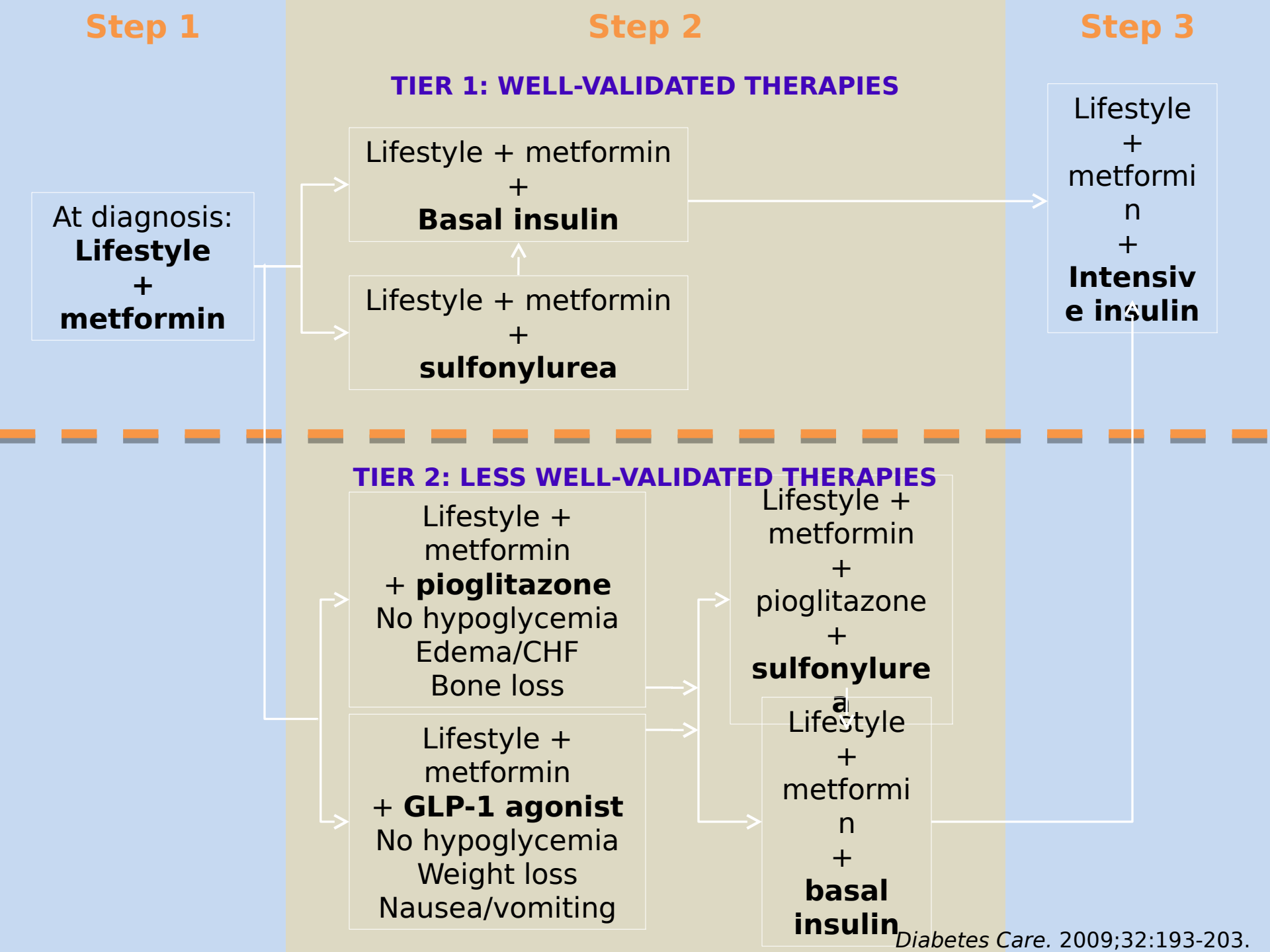
- **Utilization Management**
  - Narcotic analgesics — Fentanyl step-edit expanded to all high-potent opioids
  - Fenofibrate meltdose (Fenoglide) — BCF removal
- **Other Issues: Prior Authorization**
  - Simvastatin/niacin extended release (Simcor) 40 mg
  - Multiple Sclerosis Drugs — fingolimod (Gilenya)
  - PPI/Plavix interaction

Uniform Formulary Class Reviews: Non-Insulin Diabetes Drug Class

Non-Insulin Diabetes Agents

Incretin Mimetics	DPP-4 Inhibitors	Sitagliptin (Januvia)* Saxagliptin (Onglyza)*+
	GLP1RAs	Exenatide (Byetta) Liraglutide (Victoza)
Insulin Sensitizers	Biguanides	Metformin (Glucophage)+
	TZDs	Pioglitazone (Actos)*+ Rosiglitazone (Avandia)*+
Insulin Secretagogues	Sulfonylureas	Glipizide*+ Glimepiride Glyburide
	Meglitinides	Nateglinide (Starlix) Repaglinide (Prandin)*
Other	AGIs	Acarbose (Precose) Miglitol (Glyset)
	Amylin Agonist	Pramlintide (Symlin)

* Combination with metformin
+ XR formulation



Diabetes Care. 2009;32:193-203.

November 2010 UF Decisions

BCF drugs — MTFs must have on formulary	MTFs may have on formulary	MTFs must not have on formulary
DPP-4 Inhibitors • Sitagliptin (Januvia) • Sitagliptin/Metformin (Janumet) Sulfonylureas • Glipizide • Glyburide • Glyburide micronized Biguanides • Metformin IR - 500mg, 850mg, 1000mg • Metformin XR - 500mg, 750mg	DPP-4 Inhibitors • Saxagliptin (Onglyza) GLP1RAs • Exenatide (Byetta) • Liraglutide (Victoza) TZDs • Pioglitazone (Actos) • Pioglitazone/Glimepiride (Duetact) • Pioglitazone/Metformin (Actoplus Met) • Pioglitazone/Metformin XR (Actoplus Met XR) Sulfonylureas • Glipizide ER • Glimepiride • Glipizide/Metformin • Glyburide/Metformin • Chlorpropamide Meglitinides • Nateglinide • Repaglinide (Prandin) AGIs • Acarbose • Miglitol (Glyset) Amylin Agonist • Pramlintide (Symlin) vials and pre-filled pens	Biguanides • Fortamet (500mg, 1000mg) • Glumetza (500mg, 1000mg) TZDs • Rosiglitazone (Avandia) • Rosiglitazone/Metformin (Avandamet) • Rosiglitazone/Glimepiride (Avandaryl)

Alpha-glucosidase Inhibitors (AGIs)

Class Definition

Characteristic	Acarbose (Precose)	Miglitol (Glyset)
Type of Drug	Non-Insulin Diabetes Agent, AGIs	Non-Insulin Diabetes Agent, AGIs
Generic Available	Yes	No
FDA Indications	Adjunct to diet and exercise to lower blood glucose in patients with Type 2 diabetes mellitus (non-insulin dependent, NIDDM)	Type 2 diabetes mellitus (non-insulin dependent, NIDDM): Monotherapy as an adjunct to diet to improve glycemic control in patients with Type 2 DM whose hyperglycemia cannot be managed with diet alone Combination therapy with a sulfonylurea when diet plus either miglitol or a sulfonylurea alone does not result in adequate glycemic control; the effect of miglitol to enhance glycemic control is additive to that of sulfonylureas when used in combination

Overall Clinical Effectiveness Conclusion

- **Efficacy:**
  - No statistical differences in mortality outcomes
  - Statistical and clinical differences in A1C as compared to placebo; average A1C lowering vs placebo: acarbose -0.77%, miglitol 0.68%
  - Acarbose had a statistically significant difference in PPG while miglitol did not
  - Acarbose had statistically and clinically significant reduction in A1C when combined with metformin
  - Miglitol had statistically significant reduction in A1C; questionable for clinical significance since it did not reach 0.5% reduction in one study
- **Safety/tolerability**
  - No clinically relevant differences between the two agents in terms of safety/tolerability
  - There are significant GI side effects with these agents

Amylin Agonist

Amylin Agonist

- Synthetic analog of human amylin
- Indication: Patients with Type 1 or 2 DM uncontrolled on QID insulin therapy
- Administration
  - Given SQ 15 minutes prior to meals
  - Do not mix with other insulins
  - Patient must give multiple injections at separate times
  - When vials are used, must draw up mcg doses in unit syringes
- Caution: Initially decrease insulin doses by 50% to avoid hypoglycemia

Overall Clinical Effectiveness Conclusion

- Pramlintide is used in combination with insulin therapy and is typically dosed TID or QID
- Pramlintide lowered HbA1c across all doses when combined with insulin compared to placebo
  - -0.1% to -0.39% in T1DM and -0.3% to -0.6% in Type 2 DM
- The risk of hypoglycemia is increased when concomitantly administered with insulin; insulin doses should be decreased by 50%

Biguanides

Drugs in the Class

Brand (manufacturer)	Generic	Generic availability	Strengths & Formulations	FDA approval	Patent Expiration	Dosing
Immediate Release						
Glucophage (BMS)	Metformin	Yes	500 mg, 850 mg, 1000 mg Tabs	3/3/1995	----	BID
Riomet (Ranbaxy)	Metformin	No	500 mg/5 ml Solution	9/11/2003	2023	BID
Extended Release						
Glucophage XR (BMS)	Metformin ER	Yes	500 mg, 750 mg Tabs	10/13/2000	---	QD
Fortamet ER (Shionogi)	Metformin	No	500 mg, 1000 mg Tabs	4/28/2004	2018-2021	QD
Glumetza (Depomed)	Metformin	No	500 mg, 1000 mg Tabs	6/3/2005	2016-2021	QD

Efficacy Outcomes Trials:
UK Prospective Diabetes Study (UKPDS)

- Primary Analysis
  - N=753; overweight, Type 2 DM; mean age=53 yrs; 10.7-yr duration
    - Randomized: intensive therapy with metformin vs conventional
    - Outcome: FPG < 108
- Results
  - Patients on metformin, compared to diet alone had a risk reduction of 32% (95% CI 13-47, p=0.002) for any diabetes-related endpoint
  - 42% (95% CI 9-63, p=0.017) for diabetes-related death
  - 36% (95% CI 9-55, p=0.011) for all-cause mortality

Overall Clinical Effectiveness Conclusion

- Metformin decreases HbA1c by 1.5%–2%
- The UKPDS outcomes trial established metformin efficacy in obese DM patients vs diet at decreasing the risk for any diabetes-related endpoint (p=0.002)
- A systematic review from AHRQ shows metformin and sulfonylurea have similar or superior effects on glycemic control, lipids, and other intermediate endpoints compared with TZDs, AGIs, and meglitinides
- No evidence to suggest that differences in the long- acting release formulations of Glumetza and Fortamet confer any benefits in efficacy or safety
- Adverse effect profile of metformin is well-known with regards to renal contraindications

Dipeptidyl-peptidase 4 (DPP-4) Inhibitors

Drugs in the Class

Active Ingredient	Brand	Strengths
Sitagliptin	Januvia (Merck)	25mg, 50mg, 100mg
Sitagliptin/ Metformin	Janumet (Merck)	50mg/500mg, 50mg/1000mg
Saxagliptin	Onglyza (BMS)	2.5mg, 5mg
Saxagliptin/ Metformin ER	Kombiglyze XR	2.5mg/1000mg 5mg/500mg 5mg/1000mg

Glycemic Control Clinical Conclusion

- Monotherapy
  - Monotherapy with sitagliptin 100mg daily ↓ mean A1c by 0.6–0.79% (mean difference from PBO)
  - Monotherapy with saxagliptin ↓ mean A1c by 0.4-0.7%
- Adding sitagliptin to Met or PIO alone ↓ A1c by 0.5-0.9%
- Fixed-dose combination SIT50/Met1000 BID ↓ A1c by 1.9%
- When compared head-to-head, sitagliptin lowered A1c by ~ 0.1% more than saxagliptin

Weight
Clinical Conclusion

Sitagliptin Study	Treatment Arms	Change in Weight (kg)
Nonaka	SIT 100mg PBO	-0.1kg -0.7kg
Raz	SIT 100mg SIT 200mg PBO	-0.6kg -0.2kg -0.7kg
Aschner	SIT 100mg SIT 200mg PBO	-0.2kg -0.1kg -1.1kg
Charbonnel	SIT + Met Met	-0.7kg -0.6kg
Rosenstock	SIT + PIO PIO	+1.8kg +1.5kg
Stein	SIT + Met GLIP + Met	-1.3kg +1.2kg

Saxagliptin Study	Treatment Arms	Change in Weight (kg)
Rosenstock	SAX 2.5mg SAX 5mg PBO	-0.94 -0.23 -1.03
Jadzinsky	SAX 5mg + MET MET	-1.8 -1.6
DeFronzo	SAX 2.5mg + MET SAX 5mg + MET PBO + MET	-1.43 -0.87 -0.92
Chacra	SAX 2.5mg + GLY 7.5mg SAX 5mg + GLY 7.5mg PBO + GLY (up titrated)	+0.7 +0.8 +0.3
Hollander	SAX 2.5mg + TZD SAX 5mg + TZD PBO + TZD	+1.3 +1.4 +0.9

- DPP-4 inhibitors, as monotherapy or combined with metformin, are weight neutral
- When combined with sulfonylureas and TZDs, may have weight gain

Safety/Tolerability
FDA Safety Warnings

- **Pancreatitis (posted 9/25/09)**
  - October 2006 – February 2009
  - 88 post-marketing cases of acute pancreatitis have been reported with sitagliptin to the FDA
  - 2 cases of hemorrhagic or necrotizing pancreatitis
  - Recommendation
    - Monitor patients for development of pancreatitis after initiation or dose increases
    - Discontinue if pancreatitis is suspected
    - Use with caution and with appropriate monitoring in patients with a history of pancreatitis

Overall Clinical Effectiveness Conclusion

- Sitagliptin and saxagliptin have similar A1c lowering effect when used as monotherapy ~0.4-0.79%
- Sitagliptin fixed-dose combination with metformin provides a 1.9% decrease in A1c from baseline
- One head-to-head trial did not show clinically significant relevant differences in efficacy or safety between sitagliptin and saxagliptin
- DPP-4 inhibitors are weight neutral, lipid neutral, and have minimal impact on blood pressure
- DPP-4 inhibitors are generally well-tolerated, have few side effects, and few drug interactions
- While not currently in the ADA treatment algorithm, DPP-4 inhibitors are an option to help patients reach their A1c goal

Glucagon-like Peptide-1 Receptor Agonists (GLP1RAs)

Drugs in the Class

Active Ingredient	Brand (Manufacturer)	Strengths
Exenatide	Byetta (Amylin)	5mcg, 10 mcg (2 pens)
Liraglutide	Victoza (Novo Nordisk)	0.6mg, 1.2mg, 1.8mg (1 pen)

Other Indications

- **Both agents**
  - Ongoing studies for the treatment of obesity in non-diabetic patients
  - Currently, the DoD has a PA in place to prevent their use for obesity
  - Being studied in adolescents with Type 2 DM
- **Exenatide**
  - Being studied to prevent weight gain associated with atypical antipsychotic use in obese adults
  - Studies in adolescents with Type 2 DM in conjunction with insulin vs pramlintide with insulin

Exenatide
FDA Safety Warnings

- **Altered renal function (posted 11/02/09)**
  - April 2005 – October 2008
  - 78 post-marketing cases of altered kidney function have been reported with exenatide to the FDA
    - 62 cases of acute renal failure and 16 cases of renal insufficiency
  - Recommendation and labeling changes
    - Should not be used in severe renal impairment (ClCr < 30 ml/min) or ESRD
    - Use caution when starting or increasing doses of exenatide from 5 to 10 mcg in pts with mod renal impairment (ClCr = 30-50 ml/min)
    - Providers should monitor patients carefully for the development of kidney dysfunction

www.fda.gov/safety/medwatch/safetyinformation. Accessed 7 Nov

Liraglutide
Warnings & Precautions

- **Liraglutide**
  - Contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2
- **Black Box Warning**
  - Risk of thyroid c-cell tumors

Overall Clinical Effectiveness Conclusion

- GLP1RAs offer another option for add-on therapy when oral agents (i.e., metformin, sulfonylureas, TZDs) no longer provide adequate glycemic control
- Exenatide and liraglutide, when added to metformin and/or sulfonylurea, lower A1c by ~ 0.8%–1.3%
- Liraglutide appears to have more of an effect on FPG than PPG due to its longer duration of action while exenatide has a greater effect on PPG
- There are no published trials with either medication that assess clinical outcomes

Overall Clinical Effectiveness Conclusion

- Both agents may produce antibodies however most patients' glycemic control is unaffected
- Appropriate screening and monitoring of patients can limit post-marketing cases of pancreatitis, renal dysfunction, multiple endocrine neoplasia syndrome type 2, and thyroid neoplasms
- Liraglutide's once daily dosing is an additional advantage
- There is no evidence of clinically relevant differences in efficacy between exenatide and liraglutide

Meglitinides

Drugs in the Class

Characteristic	Nateglinide (Starlix)	Repaglinide (Prandin)	Repaglinide and Metformin (PrandiMet)
Type of Drug	Non-Insulin Diabetes Agent, Meglitinide Derivative	Non-Insulin Diabetes Agent, Meglitinide Derivative	Non-Insulin Diabetes Agent, Meglitinide Derivative
FDA Indications	Management of Type 2 DM (non-insulin dependent, NIDDM)	Management of Type 2 DM (non-insulin dependent, NIDDM)	Management of Type 2 DM (non-insulin dependent, NIDDM)

Overall Clinical Effectiveness Conclusion

- Average A1C reduction within the class:
  - Repaglinide 0.1% to 2.1%
  - Nateglinide up to 0.2% to 0.6%
  - Repaglinide + metformin: A1C reduction -1.4% vs metformin -0.3%
- In head-to-head studies, repaglinide reduced A1C more than nateglinide. It is difficult to determine the clinical significance of this based on the quality of the two studies alone.
- No clear advantage in terms of safety/tolerability for one drug over the other

Sulfonylureas

Drugs in Class

Generic	Brand	Starting Dose	Generics Available
1st Generation			
Chlorpropamide	Diabenese	250 mg QD	Yes
Tolazamide	Tolinase (D/C)	100 to 250 mg QD	Yes
Tolbutamide	Orinase (D/C)	1000 to 2000 mg QD	Yes
2nd Generation			
Glimepiride	Amaryl	1 to 2 mg QD	Yes
Glipizide	Glucotrol	5 mg QD or div BID	Yes
Glipizide ER	Glucotrol XL	5 mg QD	Yes
Glyburide	Diabeta, Micronase	2.5 to 5 mg QD	Yes
Glyburide, micronized	Glynase, PresTab	1.5 to 3 mg QD	Yes
Combination Sulfonylureas			
Glipizide/Met	Metaglip	2.5 mg/ 250 mg QD	Yes
Glyburide/Met	Glucovance	1.25 mg/250 mg QD	Yes

Clinical Pearls

- Dose ceiling effect for class
  - Max doses do not improve glucose control
  - Risk of increasing hypoglycemia
- Glipizide
  - May use for renal impairment
- Glyburide
  - May use in gestational diabetes
- Glynase Press Tab (glyburide)
  - Micronized (smaller particle size), □ absorption
- Amaryl (glimepiride)
  - A true q24h drug

Sulfonylurea Efficacy UKPDS 33

- Results
  - Over 10 yrs, HbA1c was 7.0% (6.2-8.2) in the intensive grp compared with 7.9% (6.9-8.8) in the conventional grp — an 11% reduction ($p<0.0001$)
  - The intensive treatment grp had a 25% reduction in risk of microvascular endpoints
  - Inconclusive evidence of a 16% risk reduction ($p=0.052$) for myocardial infarction
  - Diabetes-related mortality and all-cause mortality did not differ between the intensive and conventional grps

Overall Clinical Effectiveness Conclusion

- Results from the UKPDS, showed the risk in the intensive group was 12% lower (95% CI 1-21, p=0.029) compared with the conventional group for any diabetes-related endpoint
- Patients in the intensive group had more hypoglycemic episodes than those in the conventional group ($p<0.0001$)
- Weight gain was significantly higher in the intensive group than in the conventional group ($p<0.001$)

Thiazolidinediones (TZDs)

Drugs in the Class

Generic	Brand (Manufacturer)	Initial Dosing
TZD Parent Compounds		
Rosiglitazone	Avandia (GlaxoSmithKline)	4mg QD
Pioglitazone	Actos (Takeda)	15 mg QD
TZD Combination Products		
Rosiglitazone / metformin	Avandamet (GlaxoSmithKline)	2 mg/500 mg QD-BID
Rosiglitazone / glimepiride	Avandaryl (GlaxoSmithKline)	4 mg/1 mg QD or 4 mg/2 mg QD
Pioglitazone / metformin	Actoplus Met (Takeda)	Initial dose based on current dose of pioglitazone and/or metformin
Pioglitazne/ metformin XL	Actoplus Met XR (Takeda)	Initial dose based on current dose of pioglitazone and/or metformin
Pioglitazone / glimepiride	Duetact (Takeda)	Initial dose based on current dose of pioglitazone and/or sulfonylurea

Efficacy Conclusion

- A meta-analysis by Chiquette et al. showed that for TZD monotherapy or combination therapy with metformin, sulfonylurea, or insulin, versus placebo, both agents have similar glycemic control. Both agents were superior to placebo and both agents in combination therapy were superior to montherapy.
- In 2 head-to-head trials, there was no difference between the agents in change from baseline A1C or FPG.

Current Black Box Warning

- Black Box Warning
  - Rosiglitzone: congestive heart failure and myocardial ischemia
  - Pioglitazone: congestive heart failure

Avandia Decision Summary

- On Sept 23, 2010, FDA announced restriction of Avandia to patients with Type 2 DM who cannot control their diabetes on other meds
- Avandia will remain on the U.S. market under the following conditions:
  - The manufacturer undertakes a restricted access program under a Risk Evaluation and Mitigation Strategy (REMS) with measures to ensure safe use
  - The manufacturer commissions an independent re-adjudication of the RECORD study
  - The TIDE trial is placed on full clinical hold

Rosiglitazone Restricted Access Program

- The manufacturer undertakes a restricted access program under a REMS with measures to ensure safe use, including
  - Provision of complete risk information to each patient and documentation in their medical record that the information has been received and understood
  - Documentation from health care providers that each patient receiving rosiglitazone falls into one of two categories:
    - Patients taking rosiglitazone, or
    - Patients not taking rosiglitazone who are unable to achieve glycemic control on other medications and decide not to take pioglitazone for medical reasons (per provider)
  - Documentation from health care providers that the risk information has been shared with each patient
  - Physician, patient, and pharmacist enrollment

Overall Clinical Effectiveness Conclusion

- Rosiglitazone and pioglitazone have similar effects at lowering HbA1c
- Average HbA1c lowering is 0.5% to 1%
- Rosiglitazone is associated with increased CV death, which has not been seen with pioglitazone
- Both agents associated with edema, weight gain, and heart failure
- Rosiglitazone confers no therapeutic advantage over pioglitazone

Non-Insulin DM Drugs
Step Therapy Set Up

DM Step Therapy Set Up

Subclasses	Prescribed Medication	Step 1 Look-Back (180 days)	Message to Pharmacy
DPP-4s	Onglyza Januvia Janumet	Metformin or Sulfonylureas	Must try Metformin or a Sulfonylurea first.
TZDs	Actos Avandia Actos Plus Met		
GLP1RAs	Byetta Victoza		
Meglitinides	Prandin Prandimet Starlix		
AGIs	Precose Glyset		
Amylin Agonist	Symlin	Lispro insulin or Glulisine insulin or Aspart insulin	Must try lispro insulin or glulisine insulin or aspart insulin first.

DM Step Therapy Set Up

Subclasses	Prescribed Medication	Step 1 Look-Back (180 days)	Step 2 Look-Back (180 days)	Message to Pharmacy
GLP1RAs	Byetta	Metformin or Sulfonylureas		Must try Metformin or a Sulfonylurea first.
	Victoza	Metformin or Sulfonylureas	Byetta	Must try Metformin or a Sulfonylurea first and Byetta.

New Drugs in Previously Reviewed Classes

November 2010 UF Decisions

New Drugs	BCF drugs MTFs must have on formulary	UF medication MTFs may have on formulary	NF medication MTFs must not have on formulary
Doxepin tablets (Silenor)		UF	
Estradiol valerate/dienogest (Natazia)			NF
Fenofibric acid tablets (Fibricor)			NF
Hydromorphone hydrochloride (HCl) Extended Release tablets (Exalgo)		UF	
Mometasone/formoterol oral inhaler (Dulera)		UF	
Pitavastatin tablets (Livalo)			NF

Doxepin (Silenor)

Class Definition

Generic	Brand (Manufacturer)	Strengths & Formulations	Scheduled Status	FDA Approval Date	Patent Expiration	Generic Available
Doxepin	Silenor (Somaxon)	3, 6mg tablets	-	Mar 2010	2013-2015	No
Zolpidem SL	Edluar (Meda)	5,10 mg SL tablets	C-IV	Mar 2009	Sep 2018	No
Zolpidem	Ambien (Sanofi-Aventis)	5, 10 mg tablets	C-IV	Dec 1992	Apr 2007	Yes
Zolpidem ER	Ambien CR (Sanofi-Aventis)	6.25, 12.5 tablets	C-IV	Sep 2005	Oct 2010	Yes/No
Zaleplon	Sonata (King)	5, 10 mg capsules	C-IV	Aug 1999	Jun 2008	Yes
Eszopiclone	Lunesta (Sepracor)	1, 2, 3 mg tablets	C-IV	Dec 2004	Jan 2012	No
Ramelteon	Rozerem (Takeda)	8 mg tablet	-	Jul 2005	Mar 2017	No

Place in Therapy

- Silenor is indicated for the treatment of Sleep Maintenance Insomnia in adults and elderly patients
- It may be used as long- or short-term therapy
- It is a nonscheduled alternative therapy in this class

Overall Clinical Effectiveness Conclusion

- Based on clinical efficacy alone, Doxepin (Silenor) was effective at reducing objective and subjective WASO and increasing sleep efficiency in adults and the elderly, allowing 7-8 hours of TST/night.
- Doxepin (Silenor) does not exhibit tolerance, abuse, or withdrawal characteristics; it is a nonscheduled medication.
- Doxepin (Silenor) must be taken on an empty stomach, ideally 3 hours after eating.
- Doxepin (Silenor) appears to be safe and well tolerated at recommended doses and does not exhibit rebound insomnia.
- Doxepin (Silenor) does appear to have clinical advantages over existing newer insomnia agents for UF placement.

Estradiol valerate and dienogest (Natazia)

Background

- Natazia is the first combination oral contraceptive product in the United States that utilizes:
  - Estradiol valerate (EV) in an oral form
    - Synthetic prodrug of 17ß-estradiol
  - A new progestin called dienogest
    - Structurally related to the norethindrone family of testosterone derivatives
    - Selective progestin
      - No androgenic, estrogenic, glucocorticoid, and mineralocorticoid activities
  - 4-phasic active drug regimen

Overall Clinical Effectiveness Conclusion

- Based on 2 open-label trials, Natazia is effective at preventing pregnancy
- The bleeding and cycle control for Natazia is comparable to 20 mcg ethinyl estradiol/100 mg levonorgestrel with slight decrease in withdrawal bleeding and spotting episodes due to the shorter number of hormone-free days
  (2 with Natazia vs 7 with the comparator)
- Similar safety profiles as other oral contraceptives
- No evidence that the new estrogen and progesterone offer additional benefits
- The purported benefits of 4-phasic contraception remain to be established
- Currently, there is no evidence of clinically relevant benefits of Natazia over other combination oral contraceptives; long-term safety data is not available

Fenofibric acid (Fibricor)

Background

Parameter	Comments
Type of Drug	• Contains fenofibric acid which is the active form of fenofibrate
FDA Approval Date	• Approved August 2009; 505(b)(2)
FDA Indications	• ↓TG in patients with severe hypertriglyceridemia • ↓LDL, TC, TG, and Apo B, ↑HDL in patients with primary hyperlipidemia or mixed dyslipidemia
Strengths	• 35 mg and 105 mg tablets
Dosing	• 35 to 105 mg once daily; max 105 mg • May take without regard to meals
Mechanism of Action	• Active moiety and a peroxisome proliferator alpha receptor (PPARα) activator → activates lipoprotein lipase

Overall Clinical Effectiveness Conclusion

- Fibricor contains fenofibric acid, the active ingredient of Trilipix, and is the active metabolite of fenofibrate.
- It was approved under the FDA 505(b)(2) approval process using efficacy and safety data for Tricor.
- There is no evidence to suggest clinically relevant differences exist between Fibricor and other fenofibrate formulations.
  - Fibricor contains the same active ingredient in other fenofibrates and is bioequivalent.
- In terms of safety/tolerability, Fibricor is comparable to other fenofibrates.
- Fibricor does not have any advantage over Trilipix and Tricor in terms of dosing and administration, packaging, storage, and handling requirements.
- Fibricor is another fenofibrate option for patients, but does not have compelling clinical advantages over the current fenofibrate products on the Uniform Formulary.

Hydromorphone Hydrochloride (HCl) Extended Release Tablets (Exalgo)

Background

- Type of drug
  - Centrally acting mu-opioid agonist (hydromorphone) with extended release properties
- UF drug class
  - Narcotic analgesics — UF review in Feb 2007
    - High potency (Schedule II) single analgesic agent
- FDA-approved indications
  - Management of mod. to severe pain in opioid-tolerant patients requiring continuous, around-the-clock analgesia for an extended period of time

Background

- Alcohol Effect:
  - Studies by mfg showed no dose-dumping
  - Peak hydromorphone concentration increased up to 31%
  - No effect on total drug exposure
  - Avoid alcohol due to additive CNS effects and respiratory depression

Overall Clinical Effectiveness Conclusion

- Exalgo has demonstrated efficacy superior to placebo in the treatment of chronic low back pain.
- It is restricted to opioid-tolerant patients and lag-time in pain relief must be factored into treatment plan.
- General safety profile is similar to that of other high potency narcotic analgesics
  - Possible gastrointestinal AEs related to the OROS delivery system
- Exalgo is the only ER formulation of hydromorphone currently marketed.

Mometasone/Formoterol Oral Inhaler (Dulera)

Drugs in the Class

Generic Name	U.S. Trade Name	Manufacturer	Dosage Form/Device	Strength (mcg)	Starting Dose	Labeled Uses
Mometasone/ Formoterol	Dulera	Merck	pMDI	100/5 200/5	2 puff s BID	long-term, BID asthma tx >12 y/o
Fluticasone/ Salmeterol	Advair Discus	GlaxoSmithKline	DPI	100/50 250/50 500/50	1 puff BID	long-term, BID asthma tx ≥4 y/o
Fluticasone/ Salmeterol	Advair HFA	GlaxoSmithKline	pMDI (HFA)	45/21 115/21 230/21	2 puffs BID	long-term, BID asthma tx ≥4y/o
Budesonide/ Formoterol	Symbicort	AstraZeneca	pMDI (HFA)	80/4.5 160/4.5	2 puffs BID	long-term asthma tx ≥12 y/o

Place in Therapy

- Guidelines recommend the addition of inhaled corticosteroids (ICS)/long-acting beta agonist (LABA) combination therapy in patients with persistent asthma not controlled on medium- to high-dose ICS

- Dulera provides the third ICS/LABA option available in the United States

Overall Clinical Effectiveness Conclusion

- For asthma, there are no clinically relevant differences in efficacy between Advair, Symbicort and Dulera
- All FDA approved ICS/LABA inhalers contain the same black box warning
- The formoterol has a faster onset of action than the salmeterol. Although Fomoterol has been used in other countries as a rescue medication, it is not approved in the US for this purpose
- All three products dosed BID. All three inhalers have dose counters. None contain CFCs
- Available ICS/LABA inhalers appear be highly interchangeable based on historical measures of effect

Pitavastatin tablets (Livalo)

Background

Parameter	Comments
Type of Drug	• Antilipidemic-1s (Statins)
FDA Indications	• Approved August 3, 2009 • Primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total–C, LDL-C, Apo B, TG, or to increase HDL-C
Strengths	• 1mg, 2mg, 4mg tablets
Dosing	• Once a day, with or without food, any time of day
Kinetics	• Metabolized by UGT1A3 and UGT2B7; minimal via CYP2C9 and CYP2C8 • Excreted in the urine (15%) and feces (79%)
Mechanism of Action	• Inhibition of HMG-CoA reductase

Overall Clinical Effectiveness Conclusion

- No clinical outcome studies with pitavastatin
- No clinically significant advantage in efficacy for pitavastatin at 1–4mg over low-to-moderate doses of pravastatin, atorvastatin, and simvastatin based on RCTs
- No clinically significant advantage in terms of safety/tolerability over the statin comparators based on RCTs
- No clinically significant advantage in terms of drug-drug interaction profile over similar statins based on pharmacokinetic profile review

Utilization Management
Fingolimod (Gilenya)

Background

- Type of Drug:
  - Gilenya is an oral sphingosine 1-phosphate receptor modulator
  - The 1st oral disease-modifying agent for multiple sclerosis (MS-DMD)
- FDA Approval Date: September 22, 2010
- FDA-approved Indication:
  - Treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability
- Dosing:
  - 0.5 mg orally once daily, with or without food

Utilization Management

- **Considerations for MHS**
  - Recommend PA to restrict use to the approved indications
    - Possibility that Gilenya may be used in combination with the injectable MS-DMD given its unique mechanism of action
  - PA with explicit criteria for use
    - Documented diagnosis of relapsing forms of MS
    - No current use of interferon alpha/beta or Copaxone

Review of February 2011 P&T Activities

Dave Meade, PharmD, BCPS
Clinical Pharmacist

February 2011
DoD P&T Committee Meeting

- **Uniform Formulary Class Reviews**
  - Gastrointestinal-1 Agents (GI-1s)
  - Pancreatic Enzyme Products (PEPs)
  - Antilipidemic-2 Agents (LIP-2s)

February 2011
DoD P&T Committee Meeting

- **New Drugs in Previously Reviewed Classes**
  - Aliskiren/amlodipine (Tekamlo)
  - Amlodipine/olmesartan/hydrochlorothiazide (Tribenzor)
  - Self-monitoring Blood Glucose System Test Strips and Meters
  - Donepezil (Aricept 23 mg)
  - Ondansetron Oral Soluble Film (Zuplenz)

February 2011
DoD P&T Committee Meeting

- **Utilization Management (Prior Authorization)**
  - Qualaquin (Quinine)
  - Denosumab (Xgeva)

- **Other Issues:**
  - Propoxyphene Withdrawal from the Market
  - Precision Xtra Self-monitoring Blood Glucose Test Strip Recall
  - PEC Website Update

Closing the Loop on Formulary Decisions

Shana Trice, PharmD, BCPS
Clinical Pharmacist

PORT Analysis

Use of Antidiabetics in the MHS HbA1cs at Start of Oral Antidiabetic Therapy

DoD Pharmacy Outcomes Research Team

Clinical Question: Glycemic Control at Start of Oral Antidiabetic Therapy

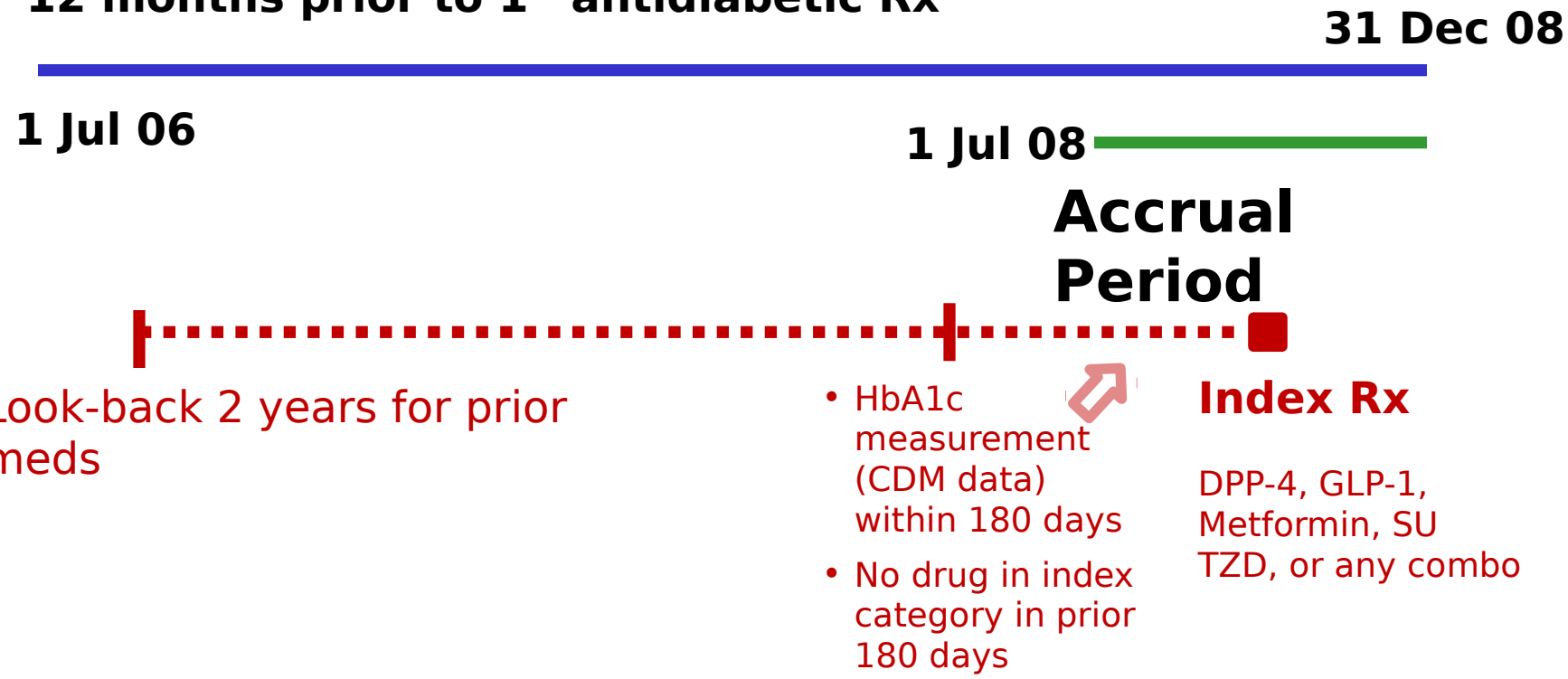
- How often are oral antidiabetics (especially the newer agents) started when they are unlikely to help patients reach their HbA1c goal (e.g., HbA1c >10)?
- Other goals
  - Assess usability of Clinical Data Mart (CDM) HbA1c data (CHCS lab data)
  - Methodology
- Exploratory data for P&T
  - Looking for patterns
  - Unadjusted and uncontrolled

Methods

Preliminary Data Pull

Look-back Period

12 months prior to 1st antidiabetic Rx


31 Dec 08
1 Jul 06
1 Jul 08
Accrual Period
Look-back 2 years for prior meds
• HbA1c measurement (CDM data) within 180 days
• No drug in index category in prior 180 days
Index Rx
DPP-4, GLP-1, Metformin, SU TZD, or any combo

- AND continuously eligible for the pharmacy benefit throughout entire time period (based on DEERs eligibility data)

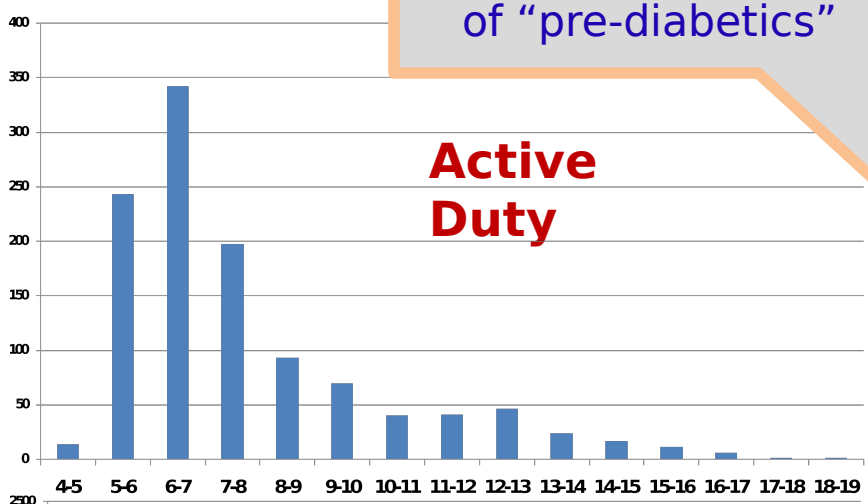
Population

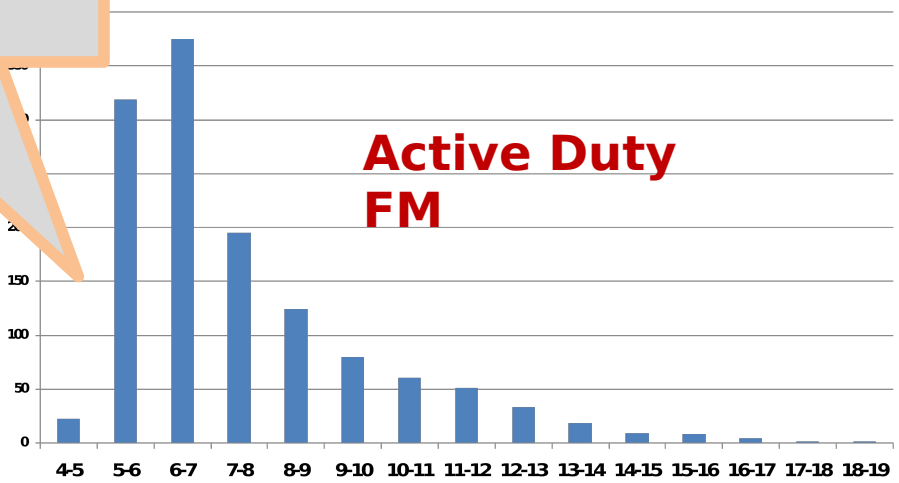
- Initial n= 13,818
  - 13,966 records; 148 with no actual HbA1c or HbA1c >20
  - Previous estimate of annual new users ~100,000 MHS-wide
  - 49.5%F, 51.5%M
  - HbA1c
    - Mean 7.7 (SD 2.0), median 7.1; min 4.3; max 19.9
  - No requirement for MTF enrollment; however, 92% were enrolled to an MTF as Prime or Plus

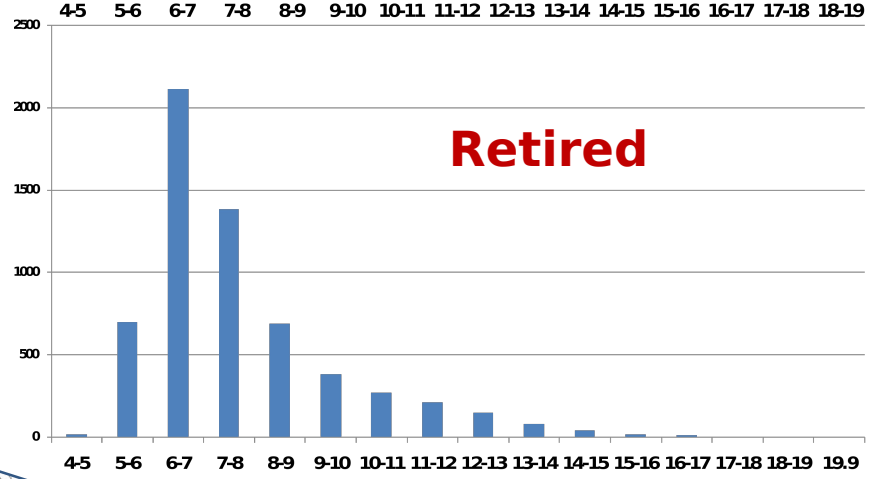
Bene Cat	#	Mean HbA1c (SD)	Median HbA1c	Mean Age (SD)
Active Duty	1146 (8.3%)	7.8 (2.5)	6.9	40.5 (7.7)
Active Duty FM	1300 (9.4%)	7.6 (2.2)	6.8	38.4 (10.2)
Retired	6057 (43.8%)	7.8 (2.0)	7.2	59.4 (9.9)
Retired FM	5315 (38.4%)	7.6 (1.9)	7.1	58.6 (11.3)

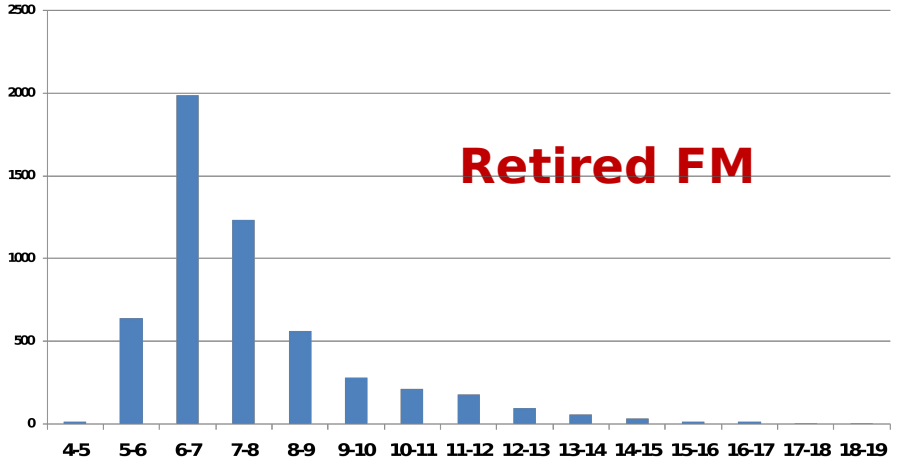
HbA1cs Among New Users of Oral Antidiabetics By Beneficiary Category

- Possibly a good number of “pre-diabetics”









New Users By Index Category

No prior use of index category last 180 days

- Using this definition, a “new metformin user” would have had no metformin (single agent) Rxs in the past 180 days, but may have had a combo containing metformin.
- The same would be true of a new “TZD/ metformin user” – no prior combo, but may have had a TZD and/or metformin
- This definition has drawbacks.

Index category	% Patients
metformin	8474 (61.3%)
sulfonylurea	1947 (14.1%)
TZD	1263 (9.1%)
DPP-4	983 (7.1%)
SU/metformin	422 (3.1%)
GLP-1	256 (1.9%)
TZD/metformin	235 (1.7%)
DPP-4/metformin	233 (1.7%)
SU/TZD	5 (<0.1%)
	13,818

New Users by Oral Antidiabetic Class

- Using this definition, a “new metformin user” would have had no metformin Rxs in the given time period, either as a single or combo agent.
- Note difference in numbers of patients between the 180-day and 2-year look-back periods
- 2 years probably a more appropriate time period

Drug Class	# with no prior use last 180 days	# with no prior use last 2 years
metformin	8339 (65.6%)	4441 (63.9%)
sulfonylurea	1900 (14.9%)	858 (12.4%)
TZD	1246 (9.8%)	580 (8.3%)
DPP-4	976 (7.7%)	860 (12.4%)
GLP-1	256 (2.0%)	208 (3.0%)
	12,717	6947

- This group used for subsequent analyses

New Users by Prior Antidiabetic Use (Last 2 Years)

- In other words, what percent of new users of each class (reading down), had prior prescriptions (last 2 years) for drugs in the specified classes (reading across)?
- Pattern generally consistent with use of use of sulfonylureas or TZDs as second agents, followed by DPP-4s, GLP-1s
- These data reflect patterns of use from 2008, however.

New Users (2-year look-back)	Met	SU	TZD	DPP-4	GLP-1	Basal insulin / NPH
Met (4441)	-	4%	3%	<1%	<1%	6%
SU (858)	56%	-	16%	3%	1%	11%
TZD (580)	62%	33%	-	3%	2%	19%
DPP-4 (860)	66%	43%	36%	-	5%	24%
GLP-1 (208)	78%	48%	50%	8%	-	36%

HbA1cs for New Users by Number of Prior Antidiabetics (Last 2 Years)

- Number of classes of antidiabetics in last 2 years

	0	1	2	3	4	5
# (n = 6947)	4611	1249	637	350	86	14
%	66%	18%	9%	5%	1%	<1%
Mean HbA1c	7.5	8	8.3	8.5	9.1	9.9

- The sample sizes get small, but note relationship. More difficult to control patients, adherence issues?

HbA1cs Among New Users of Specific Drug Classes

Drug Class	# with no prior use last 2 years	Mean HbA1c	HbA1c < 7	HbA1c >10
metformin	4441	7.6	51%	12%
sulfonylurea	858	8.0	36%	15%
TZD	580	8.1	31%	16%
DPP-4	860	7.8	33%	10%
GLP-1	208	8.1	33%	14%
	6947			

- About 10-14% of new users of DPP-4s and GLP-1s had HbA1cs>10 within 180 days before starting medication
- NOT higher than other classes
- Unknown whether given alone or with other agents (probable); good next question
- Also unable to distinguish switching between agents from adding an additional agent

HbA1cs Among New Users of Oral Antidiabetics with no prior antidiabetics, including insulin

- Note change to definition on this slide; these patients had NO previous antidiabetic Rxs in last 2 years.
- Probably closest to capturing true "new diabetics" (or pre-diabetics)

Drug Class	# with no prior use of any antidiabetic, including insulin, last 2 years	Mean HbA1c	Percent of group with HbA1c < 7	Percent of group with HbA1c >10
metformin	3943	7.5	54%	11%
sulfonylurea	306	7.8	43%	15%
TZD	152	7.4	55%	9%
DPP-4	159	7.0	58%	**2%**
GLP-1	17	6.5	76%	**6%**
	4477			

Limitations & Comments

- Population may be predisposed to better adherence; these are the patients who got their HbA1cs drawn
- Reflects practices at MTFs only
- Time period is Jul to Dec 2008; practice patterns may have shifted (esp. TZDs)
  - Use of DPP-4s and GLP-1s may have been nonformulary at many MTFs
- No diagnosis data (e.g., ICD-9 coding)
- No identification of patients

Conclusions

- HbA1c data appears usable
- HbA1cs overall appear good
- Patterns of prior use consistent with use of DPP-4s and GLP-1s as generally 3rd/4th line
- From Jul to Dec 2008, 10-14% of new users of DPP-4s and GLP-1s had HbA1cs>10 within 180 days before starting medication, comparable to other classes
  - For patients with NO prior antidiabetic use (last 2 years), rates were 2-6%, lower than with other classes
- May not represent current usage patterns
- Baseline information to look at possible changes in use when DPP-4s added to BCF

Update on Lexicomp & Epocrates

Brian Beck, PharmD
Clinical Pharmacist

Online Drug Information/Formulary Information

- **Epocrates**
  - Drug information resource
  - Contains the TRICARE Formulary
    - Displays Tiers, Step Therapy, Quantity Limits, Prior Authorization, Basic Core Formulary
  - Free web-based access www.epocrates.com
  - Free access from your mobile device

Online Drug Information/Formulary Information

- **Lexi-Comp**
  - DoD Drug Information Resource
  - Future Function
    - TRICARE Formulary
  - Available on the web and mobile devices
  - http://online.lexi.com

Procedures for Drug Recall

Heather Hellwig, PharmD, BCPS
Clinical Pharmacist

Recall Management

- Types of FDA recalls:
  - Class 1: Medications that could cause serious health problems or death
  - Class 2: Medications that might cause a temporary health problem or pose only a slight threat of serious nature
  - Class 3: Medications that are unlikely to cause any adverse health reaction, but that violate FDA labeling or manufacturing laws

Recalls to the patient level

- Recall Levels: Pharmaceutical Manufacturer > Wholesaler > Pharmacy > Patient
- Recall level is independent of the recall class
- Determine if medication/lot has been stocked
- Contacting patients
  - CHCS DUR report
  - Include patients who received the prescription during the time frame the medication was stocked
  - May/may not have received the affected lot
  - Contact via telephone and/or letter

Documenting recall actions

- Follow instructions in MMQC/FDA/Manufacturer message
- Document via DMLSS (as applicable)
- Document
  - Type of recall
  - Medication/Manufacturer/Lot number
  - Steps/procedures performed (e.g., removal from stock shelves, DUR, contacting patients)
- Storage of documentation
  - P&T minutes
  - Pharmacy department files

Inventory Levels

- Suggestions for low inventory levels caused by a recall:
  - Contact your wholesaler
  - Contact the manufacturer’s government representative
  - Contact other facilities
  - Watch for guidance from your specialty leader
  - Develop plan for how to ‘ration’ medication if necessary

Tips for Recall Management

- Subscribe to receive Medical Material Quality Control (MMQC) recall messages through e-mail at http://www.usamma.army.mil
- MMQC messages are supplied by the United States Army Medical Material Agency (USAMMA)
- Specific disposition instructions are found in each MMQC message
- Sign up to receive recalls, market withdrawals, and safety alerts from the FDA via e-mail at http://www.fda.gov/Safety/Recalls/default.htm

Update on the Drug Seeking Beneficiary (DSB) Edit

Elizabeth Hearin, PharmD, BCPS
Clinical Pharmacist

Update

- **CHCS**
  - The DSB edit is a part of CHCS Change Package 362 and was released on 2/21/11.

- **PDTS**
  - The DSB edit can be turned on and off by site through PDTS.
  - The DSB edit will be turned on for all MTF sites after beta testing that will occur in early March.
  - Beta sites: Ft. Carson and Ft. Stewart

Questions?

PEC Contact Info

- 210-295-1271 (DSN 421-1271)
  - For PEC Clinical Staff

  1-866-ASK 4 PEC (275-4732)
  - Pharmacy Operation Center
  - PECWEB@amedd.army.mil
    - Website issues
  - pdts.ameddcs@amedd.army.mil
    - Questions, assistance with PDTS, Business Objects
  - PECUF@amedd.army.mil
    - Clinical, formulary questions